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ILSI Health and Environmental Sciences Institute

Risk Assessment Methodologies (RAM) Technical Committee

I. Overview

The overall mission of the RAM committee is to augment current exposure and risk assessment methods and model development efforts through projects, workshops, and scientific symposia aimed at addressing critical issues such as data needs, data characterization, and model evaluation.

The RAM committee is currently divided into two projects: 1) Weight of Evidence in Risk Assessment and 2) Risk Assessment of Chemical Mixtures, which are described below.

II. Weight of Evidence (WOE) in Risk Assessment

A. Background

The WOE project was proposed as a topic within the existing RAM committee in 2004, and initiated by representatives from government, academic, and industry sectors, who recognized the need for a consistent, clear, credible approach to evaluating, interpreting, and evaluating data within the context of risk assessment.

B. Accomplishments

- 2005: "Weight of Evidence: A Review of Concept and Methods", by Douglas Weed, contracted by the committee, published in *Risk Analysis* (Vol. 25, No. 6, 1545-1557).
- December, 2006: International workshop attended by over 60 participants from government, industry, academia, and NGOs to discuss the current state of the practice of WOE evaluation in risk assessment in both Europe and the US, and to propose a research agenda.
- Fall, 2007: Workshop manuscript to be submitted for publication in *Risk Analysis*.
- September, 2007: Members of the committee invited to present the committee's work at the American Chemical Council LRI Dialogues in Science & Research Meeting.
- December, 2007: The committee will present a symposium on the project at the Society of Risk Analysis Annual Meeting.

C. Future Directions

- Fall 2007/Spring 2008: The committee will work on the preparation of a manuscript dealing with use of transparency in weight of evidence analysis, with the aim of raising awareness of the concept of transparency in risk assessment and providing some general transparency "principles."
- January, 2008: Project update to be provided at the winter meeting of the Toxicology Forum.
- Spring 2008: The committee will begin work on improving the integration of the human relevance mode of action (MOA) framework into risk assessment by expanding scope of the framework to examine multiple modes of action, multiple endpoints, etc. This expansion will begin by developing a tool to examine dose-response analyses, using several case studies to illustrate the framework expansion.
- Summer, 2008: The committee aims to present a session at summer, 2008 Toxicology Forum meeting.



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- October, 2008: The committee will present a symposium on the project at the 2008 Eurotox 45th Congress.

D. Anticipated Impacts

- This project has wide applicability within the US, European, and global regulatory communities, and aims to improve the science behind risk assessment.
- The initiative will facilitate a move towards consistency in regulatory approaches in the US and abroad.
- This effort has broad applicability to other HESI projects which have as a need the incorporation of weight of the evidence best practices and methodologies for data integration in risk assessment.

E. Committee Participation

- | | |
|--|------------------------|
| • Arkema, Inc. | • Health Canada |
| • Bayer CropScience | • Pfizer, Inc. |
| • California DPR | • Syngenta Ltd. |
| • Canada PMRA | • US EPA |
| • The Dow Chemical Company | • USDA |
| • The Procter & Gamble Company | • US FDA |
| • Rohm and Haas Company | • US OMB |
| • International Agency for Research on Cancer (IARC) | • University of Ottawa |
| • ExxonMobil Biomedical Sciences, Inc. | • University of Guelph |

III. Risk Assessment of Chemical Mixtures

A. Background

The development and application of risk assessment methodologies that incorporate mixtures has become increasingly widespread. Conducting mixtures risk assessments poses many challenges including the design of realistic models, collection of relevant and accurate data, adequate characterization the quality and relevance of the available data, and the interpretation and application of risk assessment results. The mixtures project within RAM aims to develop a decision-framework to facilitate the identification and evaluation of the critical questions that, if answered, will provide scientifically credible and impactful outcomes.

B. Accomplishments

- Spring, 2005: The committee determined their scope of work and proposed to examine the applicability of the toxicological threshold of concern (TTC) concept to chemical mixtures.
- March 2006: HESI representatives met with the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Mixtures Task Force and agreed to coordinate their efforts; this coordination was also recognized by IPCS, and HESI is working with both groups to coordinate potential case-study efforts based on the IPCS mixtures framework.



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- September 2007: The committee began a contracted literature review on synergy, with the aim of determining if it is possible to establish an applicable synergistic factor or other criterion/criteria that may be generally applied within a TTC-based screening approach.

C. Future Directions

- Fall, 2007/Spring 2008: The committee will begin work on selection criteria for several mixtures case studies, in coordination with ECETOC and IPCS.
- FQ 2008: Completion of synergy review study and publication of manuscript; continued work on TTC approach.
- The committee has regularly scheduled coordination calls with the ECETOC group, and is in touch with the IPCS committee representatives.
- Fall 2008: Potential case study workshop with IPCS and ECETOC.

D. Anticipated impact

- It is expected that the outcome of this project will be a globally accepted and endorsed approach to the assessment of mixtures, due to the close coordination with both IPCS and ECETOC.
- The TTC work focuses on prioritizing those environmental chemical mixtures that should be subject to in-depth risk assessment and those that are expected to be of lesser concern in order to best utilize the limited available resources. This project in particular could have a positive impact on chemical registrations and evaluations, particularly with the REACH Initiative in Europe.
- It is anticipated that the approach developed will be generally applicable to mixtures, including formulated products (pharmaceuticals, consumer products, etc.), complex mixtures, and co-exposures and environmental mixtures.
- The approach will be useful for improving interpretation of biomonitoring results and prioritization of future biomonitoring initiatives.

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| • Centers for Disease Control, ATSDR | • Pfizer, Inc. |
| • Colorado State University | • Syngenta Ltd. |
| • The Dow Chemical Company | • US EPA |
| • Imperial College London | • US FDA |
| • The Procter & Gamble Company | • University of Guelph |

September, 2007